MACVIA-ARIA Sentinel NetworK for allergic rhinitis (MASK-rhinitis): The new generation guideline implementation.

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Short title : the next generation ARIA

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Abstract

Several unmet needs have been identified in allergic rhinitis: identification of the time of onset of the pollen season, optimal control of rhinitis and comorbidities, patient stratification, multidisciplinary team for integrated care pathways, innovation in clinical trials and above all patient empowerment. MASK-rhinitis (MACVIA-ARIA Sentinel NetworK for allergic rhinitis) is a simple system centred around the patient which was devised to fill many of these gaps using Information and Communications Technology (ICT) tools and a clinical decision support system (CDSS) based on the most widely used guideline in allergic rhinitis and its asthma co-morbidity (ARIA 2015 revision). It is one of the implementation systems of the Action Plan B3 of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA). Three tools are used for the electronic monitoring of allergic diseases: a cell phone-based daily visual analogue scale (VAS) assessment of disease control, CARAT (Control of Allergic Rhinitis and Asthma Test) and the e-Allergy screening (Premedical system of early diagnosis of allergy and asthma based on online tools). These tools are combined with a clinical decision support system (CDSS) and are available in many languages. An e-CRF and an e-learning tool complete MASK. MASK is flexible and other tools can be added. It appears to be an advanced, global and integrated ICT answer for many unmet needs in allergic diseases which will improve policies and standards.

Key words: allergic rhinitis, asthma, conjunctivitis, ARIA, MACVIA-LR, visual analogue scale, ICT, clinical decision support system

Abbreviations

AHA: Active and Healthy Ageing
AIRWAYS ICPs: Integrated Care Pathways for Airway diseases
AR: Allergic rhinitis
ARIA: AR and its Impact on Asthma
CARAT: Control of Allergic Rhinitis and Asthma Test
CDSS: Clinical decision support system
EIP: European Innovation Partnership
ICP: Integrated care pathway
ICT: Information and communications technology
MACVIA-LR: Contre les Maladies Chroniques pour un VIeillissement Actif en Languedoc-Roussillon
MASK: MACVIA-ARIA Sentinel NetworK
MeDALL: Mechanisms of the Development of Allergy (FP7)
QOL: Quality of life
RAPP: RhinAsthma Patient Perspective
RCT: Randomized control trial
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
SCUAD: Severe Chronic Upper Airway Disease
U-BIOPRED: (IMI)
VAS: Visual analogue scale

Introduction

Allergic rhinitis (AR) is among the most common diseases globally (1) and ranks first in Europe (largely over 25% of the European population). It exists in all age groups, and it often starts early in life (2) and persists across the life cycle (3, 4). The burden and costs are substantial (5). It often impairs social life, work and school performance (6-8), and has a major impact on healthy ageing (9).

Several unmet needs have been identified. MASK-rhinitis is a simple system centred around the patient. It has been devised to fill many of the gaps using Information and Communications Technology (ICT) tools and a clinical decision support system (CDSS) based on the most widely used guideline in AR (ARIA) (10). It is a product of the European Innovation Partnership on Active and Healthy Ageing (11) and was launched in 15 countries in June 2015. Patient empowerment is essential to the project. MASK-rhinitis represents a novel tool to diagnose, stratify, and manage patients with AR and to assess treatment efficacy. It has the potential to have major impact on health policies and planning. In the future, the combination with biomarkers will further improve the impact of MASK-rhinitis.

MACVIA-LR (Fighting chronic diseases for active and healthy ageing, http://macvia.cr-languedocroussillon.fr) is a reference site of the European Innovation Partnership on Active and Healthy Ageing (12). It has initiated the project AIRWAYS ICPs, an integrated care pathway (ICP) for airway diseases (13).

1- Unmet needs in allergic rhinitis

1-1- Early diagnosis and management of patients with respiratory allergic diseases

Although AR is common in all age groups, it is very often overlooked and under-diagnosed, especially in pre-school children and the elderly. The Polish Presidency of the EU Council (2011) targeted chronic respiratory diseases in children to promote their early recognition, prevention and management and, ultimately, to promote AHA (9).

Clinical diagnosis is difficult and symptoms may relate to allergic and non-allergic rhinitis as well as rhinosinusitis (14). There is a need for a simple diagnostic tool.

1-2- Patient stratification

The treatment of AR is now well established. Although the majority of patients present with controlled symptoms during pharmacologic treatment, 10 to 20% of them are still uncontrolled and should be characterized as suffering from severe chronic upper airway disease (SCUAD) (15). SCUAD patients have impaired quality-of-life, sleep, school and/or work performance (16, 17).

Many AR patients are over 65 years of age. The presentation of the disease, as well as the efficacy and safety of treatments, may differ in older adults. However, data are not yet available from RCTs.

1-3- Time of onset of the allergy season

For patients allergic to pollen, knowledge of the onset of the pollen season is of vital importance in order to start their treatment as early as possible for the control of symptoms. When travelling, patients are often concerned about potential symptoms and/or bothered by symptoms outside their usual symptom 'window'. It is therefore of importance to forecast the onset of the pollen season and to characterize seasons in different places.

Pollen counts are currently proposed to assess the exposure of pollen-allergic patients. However, counts correlate often imperfectly with symptoms (18 , 19-22) since (i) they do not represent strictly allergen exposure alone (19, 23, 24), (ii) the number of pollen grains needed to elicit symptoms is not well defined and differs depending on the pollen species, (iii) there is a non-linear relationship between pollen and allergic symptoms (25, 26), and (iv) interactions between pollens and atmospheric conditions or air pollution may exist (27, 28). Furthermore, for large geographical areas, pollen samplers are sparsely located. Patients may live at a distance from the sampler and the levels of allergens in their environment may differ quite extensively from the levels detected by the sampler. Individualised pollen counts would be preferable (29) but are not feasible on a large scale. Finally, pollen counts are only available several days after the season onset.

The assessment of allergen content in the air is feasible using antibody-based methods (18, 19, 30) or the biomolecular identification of pollen genomes (31). However, sophisticated methods are required which may not account for all of the pollen species in the ambient air, and individual measurements are not feasible.

Meteorological data may, in the future, be of interest to predict the onset of the season, but more information is needed (32-35). Combining several data sources using advanced data engineering may offer advances, but this method is still complex and not available for all pollen species in many different areas (36, 37).

Internet-based surveillance systems using search engine queries (38) and social media (39) are recent techniques with the potential to extend or even substitute more costly disease surveillance systems (40). A few studies analysing online searches on pollens, rhinitis symptoms and allergies have shown associations with pollen counts (41). The analysis of online searches, in particular using Google trends, has shown potential in predicting changes in flu infections (42) and in other areas of medicine (38). Nevertheless, this type of big data analysis is just beginning (38) and more research is needed to prove its value in predicting the onset of allergic rhinitis symptoms due to the pollen season (43). Moreover, the onset of the pollen season cannot be predicted using these models.

In the meantime, other novel approaches such as a personalized pollen-related forecast (44, 45) and an ICT sentinel network based on patients' symptoms should be developed. However, these approaches need to be simple and user friendly.

1-4- Continuous management of symptoms during allergen exposure

Allergen exposure varies daily and patients with respiratory allergic symptoms need regular monitoring of their symptoms to optimize their treatment. A clinical decision support system (CDSS) may be beneficial to optimize treatment and assess disease control after commencement of the allergy season. Moreover, such a system has the potential to improve patients'compliance to treatment. Guided management of allergic diseases including asthma was found to be effective (46, 47) with clear evidence provided by the Finnish Asthma Programme (48), and the Allergy Programme (49, 50).

1-5- Co-morbidity assessment

Conjunctivitis, chronic rhinosinusitis and asthma are frequent AR comorbidities that need to be identified and treated to achieve good AR control (51). ICPs that include asthma screening and assessment, as recommended by ARIA (Allergic Rhinitis and its Impact on Asthma) (6, 7), may result in improved outcomes and should be tested. In addition, optimal AR control may facilitate the control of concomitant asthma.

1-6- Needs for a multidisciplinary team for an ICP

Integrated care pathways (ICPs) are structured multidisciplinary care plans which detail essential steps in the care of patients with a specific clinical problem (52). They promote the translation of guideline recommendations into local protocols and their subsequent application to clinical practice. An ICP forms all or part of the clinical record, documents the care given, and facilitates the evaluation of outcomes for continuous quality improvement (53). ICPs can help empower patients and their care providers (health and social). They differ from clinical practice guidelines as they focus on the quality and co-ordination of care. ICPs need to have a mechanism for recording variations/deviations from planned care. Variation from recommendations to the practice identified within an ICP should be noted as a variance (54, 55). In AR, there is a need for ICPs which combine the views of patients, pharmacists, primary care physicians, specialists and other health care professionals.

1-7- Biomarkers in respiratory allergic diseases

Biomarkers are of great importance in respiratory allergic diseases and asthma, and a large body of research is focusing on the identification and validation of biomarkers. Biomarker identification can be based on systems medicine approaches combining transcriptomics, proteomics, epigenetics and metabolomics in large patient cohorts. One recently completed EU project, MultiMod, resulted in a generally applicable strategy to integrate such data for diagnostic purposes using systems medicine principles (56). Two EU-funded projects are currently ongoing: U-BIOPRED (IMI) in severe asthma (57) and MeDALL (FP7) in allergy (58 , 59). MeDALL has already made critical observations concerning IgE biomarkers for the diagnosis and prognosis of allergic diseases (2, 60). It is hoped that these projects will help identify biomarkers to enhance personalized medicine (61, 62), and to improve patient stratification and clinical trials. Another ongoing EU project, CASyM, has generated a roadmap for the implementation of systems medicine in clinical research and practice (https://www.casym.eu/).

1-8- Innovation in clinical trials

In randomized controlled trials (RCTs), it is essential to have clarity with regards to the definitions of disease severity and control as well as co-morbidities and risk factors (e.g. smoking). RCT outcomes should be validated and standardized, so that meaningful comparisons between RCTs can be made (63). Several gaps exist in RCTs in respiratory allergy. Among them are the importance of the placebo effect and the evaluation of efficacy using a single assessment tool combining symptoms, medications and quality of life (64). Novel tools for the evaluation of RCTs on AR and its common comorbidities are needed, if possible using ICT.

1-9- Climate change effects on allergic diseases

Allergy prevalence continues to grow due to novel interactions between known allergens and other environmental factors. An increase in the prevalence and severity of allergy and asthma are anticipated due to climate changes (65). Worsening ambient air pollution and altered local and regional allergen production (66) and reduction in biodiversity may play a significant role (67). This anticipated higher allergic disease burden will affect clinical practice as well as policies and public health planning.

1-10- Patient empowerment

To satisfy patient expectations, asthma and AR should be appropriately diagnosed and controlled. Patients need to be motivated to become educated and to actively increase their own health literacy to be able to take over the responsibility of their own specific condition. Patient organizations have been involved in the design, dissemination and implementation of ARIA. ICTs can empower patients and thus enable them to define specific goals and to monitor disease status and control. It can also support the patient's decisions.

2- Tools

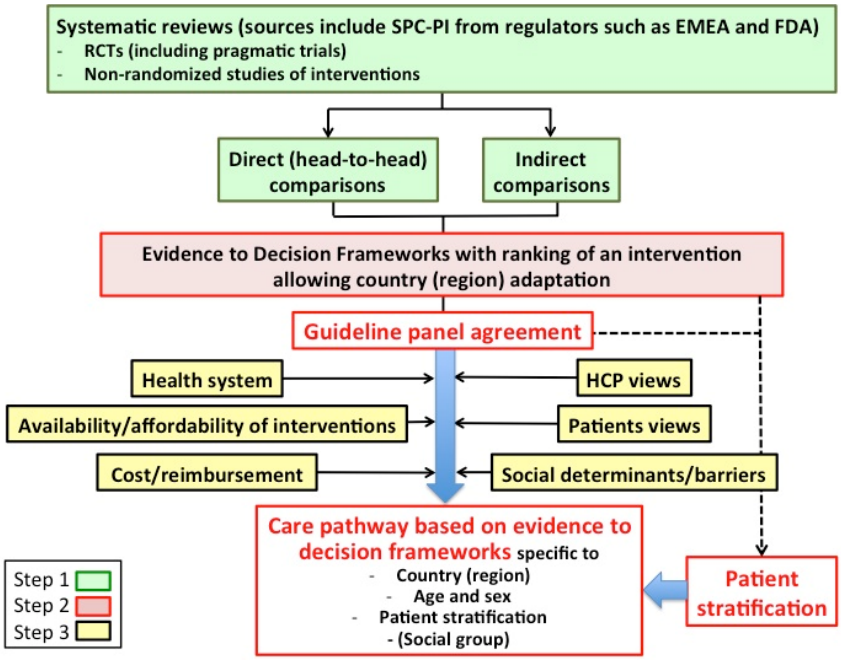
2-1- ARIA

ARIA was initiated during a WHO workshop in 1999 (published in 2001) (6, 7). The ultimate aim of ARIA is to achieve control of AR globally. ARIA has reclassified AR as mild/moderate-severe and intermittent/persistent. This classification closely reflects patients' needs and underlines the close relationship between rhinitis and asthma. A module devoted to the pharmacist exists (68). In its 2010 Revision, ARIA developed clinical practice guidelines for the management of AR and asthma co-morbidities based on GRADE (Grading of Recommendation, Assessment, Development and Evaluation) (69). ARIA is disseminated and implemented in over 60 countries of the world (10). ARIA has been endorsed by several ministries of health.

Variance has been tested and it was found that the ARIA classification of mild vs moderate-severe and intermittent vs persistent rhinitis is valid. A modified ARIA severity classification has also recently been validated as mild, moderate, and severe, both in adults (70) and children (71), although its impact on treatment stratification remains an unmet need.

The 2015 ARIA revision leading to ICPs will be finalized and presented at the AIRWAYS ICPs meeting in Lisbon July 1-2, 2015 (Figure 1).

Figure 1: ARIA 2015



2-2- Measures of allergic rhinitis control

Concepts of disease severity, activity, control and responsiveness to treatment are linked but constitute different domains (72). Control and severity are not well delineated in AR (72). Severity is the loss of function in the target(s) organs induced by disease (73). It is important to highlight that severity may vary over time and needs to be regularly re-evaluated (74). Control is the degree to which therapy goals are currently met (74)) such as glycemic control in diabetes (75), and can be assessed in patients before or during treatment to guide therapy. However, for AR, the patients' view of severity relates to the negative impact that rhinitis has upon life, control is a measure by which their symptoms are alleviated.

Measures of AR control include symptom scores, patient's self administered visual analogue scales (VAS) (16, 76-81), objective measures of nasal obstruction such as peak nasal inspiratory flow, acoustic rhinometry and rhinomanometry (82), a recent modification of the ARIA severity classification (83), patient's reported outcomes such as quality-of-life (QOL) (7, 63) scores with several items (80, 84) or composite symptom-medication scores (85). However, it is important to make the score for clinical use simple and responsive to change.

VAS is a psychometric response scale for subjective characteristics or attitudes used in a large variety of diseases. The continuous (or "analogue") aspect of VAS differentiates it from discrete scales such as the Likert scale. The sensitivity and reproducibility of VAS results are broadly very similar, although the VAS may outperform the other scales in some cases (86, 87).

In AR, VAS for all nasal symptoms appears to be sufficient to appreciate disease control (88) and is particularly relevant to primary (89) or pharmacy care (68). VAS can be used in all age groups including preschool children (guardian evaluation) (90) and the elderly (91). Furthermore, it can be used in a wide variety of languages (81, 91-97). VAS levels vary with the ARIA classification in many languages (76 , 79 , 81, 98). A VAS level of 50 mm is suggestive of moderate-severe AR (99-101)

although in some studies the cutoff was of over 60 mm (94). VAS was used to define SCUAD (16) and patients with a low VAS level after treatment had a considerably improved Rhinoconjunctivities Quality of Life Questionnaire (RQLQ) or work productivity (WPAI-AS). However, those with a level of over 50 mm had no improvement. VAS has been validated in cell phones (Acaster, personal communication).

VAS was found to be responsive to change in real life cluster randomized trials (102, 103). The minimal clinically relevant difference was set for a VAS level of 23 mm during treatment, whatever the baseline VAS level (104). A level of over 23 mm appears to be a relevant cutoff. VAS changes appear to encompass both symptoms and disease-specific QOL (88 , 104).

VAS was highly responsive to change in double-blind, placebo-controlled RCTs (92, 93, 102, 105-108). These multicenter studies in Europe and Canada showed that patients easily cope with VAS in different languages.

These studies combine to indicate that VAS may be a simple and useful tool to assess AR control and follow the efficacy of treatment.

2-3- Electronic monitoring of allergic diseases

2-3-1- e-Allergy screening: Premedical system of early diagnosis of allergy and asthma based on online tools

Late diagnosis of allergic diseases and asthma is a serious problem. Patients with the first symptoms of respiratory allergies are often misclassified in primary care. As a result, patients are either untreated or treated symptomatically, generally for a long period of time. This behaviour is detrimental to the patient, the health care system and the society as it impacts on indirect costs (5).

One solution to this problem was presented in 2011 at a conference of experts during the Polish Presidency of the EU Council (109). It is an e-Allergy - premedical system capable of providing an early diagnosis of allergy and asthma on the basis of online tools. The concept is based on a screening questionnaire with built-in algoriths to assess individual risk of allergic diseases including 24 questions. The process takes about 5 minutes. The questions are selected depending on previous responses, in order to obtain the necessary information. The result is displayed in the form of risk calculation for selected allergic diseases (asthma, allergic rhinitis, atopic dermatitis and allergy to Hymenoptera venom).

To develop the algorithm, data from the Epidemiology of Allergy in Poland (ECAP) (www.ecap.pl) were used (110). Over 20,000 people responded to the study questionnaire and almost 5,000 were subjected to additional allergological tests. Various advanced methods of statistical analysis, including an artificial neural network, have been used to develop the algorithm. The system is calibrated to maximize the effectiveness of a group of persons suffering from allergic diseases.

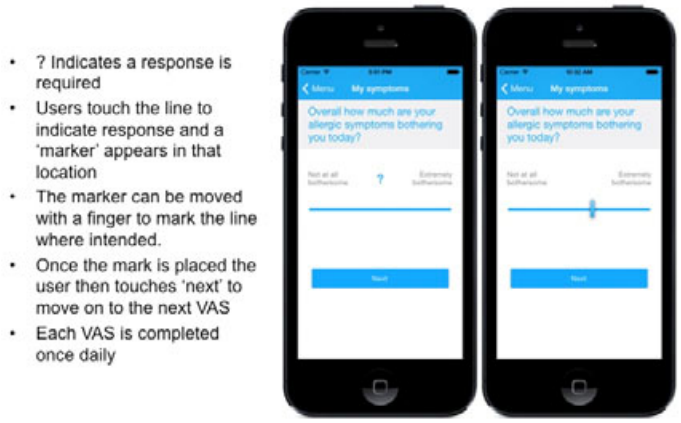
E-allergy screening can be used both by the public with suspected allergies and physicians. The initial diagnosis can lead to an evaluation. It is performed by a primary health care professional and, if needed, confirmed by a specialist. The role of e-allergy is to support, not replace, the physicians and also to speed up the process between unrecognized allergic diseases and the proper management.

2-3-2- Daily tool based on VAS using cell phones

MASK-aerobiology, approved by AIRWAYS-ICPs, is a very simple IOS/Android App. It is already available and is being expanded to other systems with interoperability. Patients selected by physicians

trained in allergy represent the sentinels for the onset of the season. The VAS represents a reliable and valid measure of rhinitis control (10, 72) (Figure 2). It can be used across the life cycle (90, 91, 111).

Figure 2: MASK aerobiology



2-3-3- CARAT

Asthma frequently occurs in association with allergic rhinitis, and a combined management approach has been suggested. The Control of Allergic Rhinitis and Asthma Test (CARAT) is the first questionnaire to assess the control of both diseases concurrently (112, 113, 114 , 115). An overall score of more than 24 indicates good control of asthma and rhinitis while a change of 4 points between two occasions indicates a clinically relevant change (115). In addition, answers to individual questions may be used to identify the specific problems of a patient (e.g. night symptoms or overuse of reliever medication). However, to have an impact on healthcare, it needs to be disseminated and adopted. At present, the adaptation of CARAT for use in different languages and cultures is being led by volunteer researchers and clinicians in 15 countries. Website and smartphone applications have been developed, and a free open model of distribution has been adopted to contribute to the dissemination of CARAT. CARAT can be used in a range of settings and circumstances in primary and secondary care for clinical, research and audit purposes, and also in ambulatory pharmacies (116). It can be used both in adults and children (117, 118) and strengthens the partnership between patients and doctors in the management of asthma and rhinitis. CARAT can be administered every 2 to 4 weeks both in paper and electronic forms (119) and represents an additional tool for the daily assessment.

2-3-4- RhinAsthma Patient Perspective

"RhinAsthma Patient Perspective (RAPP) is the first valid questionnaire to assess the individual health-related QoL of patients with asthma and rhinitis in clinical practice. It is a simple eight-question tool with good measurement properties and sensitivity to health changes. RAPP is easy to complete and to score, and the results enable immediate interpretation both for the physician and for the patient. The score, calculated by summing responses to each item, ranges from 8 (no impact on QoL) to 40 (the worst possible QoL) . A cutoff point of 15 has demonstrated the best sensitivity and specificity in discriminating the achievement of an optimal health-related QoL. A change of 2 points in the RAPP score was found to be the minimal clinical difference that patients perceived as important, either "beneficial or harmful." A new tool for smartphone has been developed (120).

2-4- Clinical decision support system

Identifying the most suitable patients for whom an intervention is appropriate is critical for the delivery of a cost-effective health system. In many diseases, the management of patients uses ICT tools including integrated care pathways, e-health and CDSS. This has made a significant improvement and has sometimes led to a change of management in health systems. A CDSS (121, 122) immediately proposes advice for (standardized) pharmacologic treatment defined by the physician during a consultation before the pollen season. Care pathways based on AIRWAYS ICPs (13) will guide the health care professional. SCUAD patients are defined as those resistant to treatment despite optimal treatment (VAS level>50%). Moreover, individual complaints of rhinitis, conjunctivitis or asthma are monitored by the system (123). Computer-analyzed VAS responses may be measured using discrete values due to the discrete nature of computer displays and VAS can be used in internet-based questionnaires (124).

2-5- Bias reduction, patient empowerment and identification of new markers through Living Lab approach

Systematically collecting and mining / analyzing data from patients' mobile phones where they can enter quantitative and qualitative information is indeed a promising use of innovative health technologies (125). This should allow, on an almost continuous mode, a long-term close monitoring of and connection to the patient. To our knowledge, this has not been addressed before by any other technology. However, a major requirement for the implementation of such clinical protocols is the validity of data (125, 126). In validating such protocols, bias by the degree of usage of devices by the patients, and bias in information input due to the context or human factors, need to be identified and eradicated; such factors are very difficult to control. The overall bias will normally be balanced by a long-term use of the application by the patient, since patients' data are always compared to their previous declarations. But it is possible and desirable to improve the results and reduce the time necessary to obtain them. Contrary to drugs, where the administration of medications to patients may be appropriately controlled during clinical trials, the usage of mobile phones, especially at home, is known to depend heavily on the usability of such devices and supported applications, on their context of use (including ongoing activities, social environment, presence of third parties), and on the constraints they impose on patients, with a strong probability of weak compliance, hazardous on/off usage or even rejection and abandon by the patients (127, 128). Similarly, the adoption of these new practices, including participation and interactions from family members or professionals, is an issue (129) .

Inappropriate and/or irregular use of the system – a social and behavioural bias - cannot be identified in the data analysis. This can compromise the scientific validity of the entire results. Furthermore, opportunities to address behavioral or psychological markers, are not seized, even when they are already identified as possible candidates by practitioners. It is therefore both mandatory and potentially highly valuable to properly address usage problems at the patients' end and to ensure the usability of a selected mobile application.

The involvement and commitment of the patients and of the health care and social professionals involved from the start and during all phases of the project is the only way to address the problem. It is highly recommended that a co-design / co-evaluation and user-centered design approach to the project is adopted (130) . This will be a lever to gain a long-term adherence of both patients and health providers. The participation of Living Labs for Health and Autonomy will secure the many tasks to be carried out throughout the project with the users and all participants. It will ensure proper usage validity of collected data right from the first phases:

- Analysis of the context of use.
- Co-design of the protocol with patients and physicians.
- Evaluation / optimization of device usability, human machine interface and adoption potential.
- Follow-up of device usage during the collecting phase.

2-6- Additional tools

An e-CRF and an e-learning tool will be added to the MACVIA-ARIA suite of instruments.

3- MASK: the global and integrated ICT answer for unmet needs in allergic rhinitis empowering patients

3-1- Electronic monitoring of the pollen season

Mobile phone messaging facilitates the management of AR (131) and chronic diseases (132, 133). By using cell phones with a touch screen, patients are geolocalized and can evaluate daily their symptoms daily by VAS (Figure 2). At the predicted time of the pollen season, based on local calendars and/or forecast models where available, patients receive an SMS and an E-mail indicating that they should monitor daily VAS for global symptoms on the dedicated mobile device. This information is coded and sent to a central database. Daily, 4 VAS (global evaluation, nasal, ocular and bronchial symptoms) are completed by the patient on a cell phone and the information is sent to a clinical decision support system (CDSS) for an optimal management to all the patients using the system. The system is initially being deployed in 13 countries with 14 languages (translation and back-translation, cultural adaptation and legal issues).

MASK-aerobiology is monitored daily and will be completed with CARAT at the onset of the pollen season and thereafter every 2 weeks (Figure 3).

Applications include information to patients and to the media with regards to the pollen season, optimal management of the patients with allergic symptoms, clinical trials, research and climate evaluation (Figure 4).

Figure 3: Combination of MASK-aerobiology, CARAT and CDSS

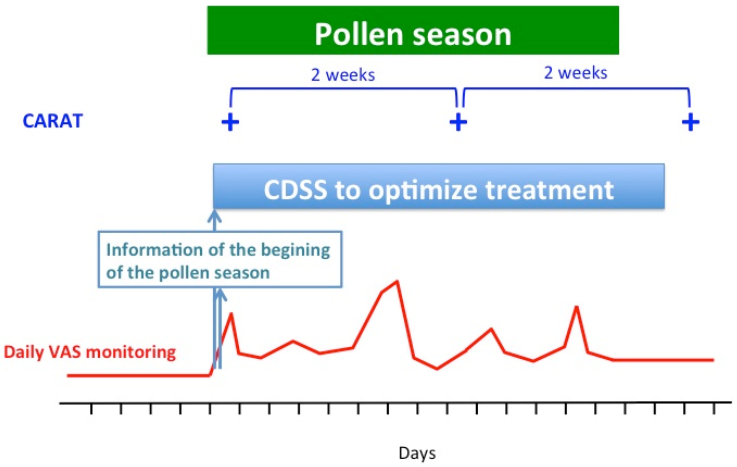
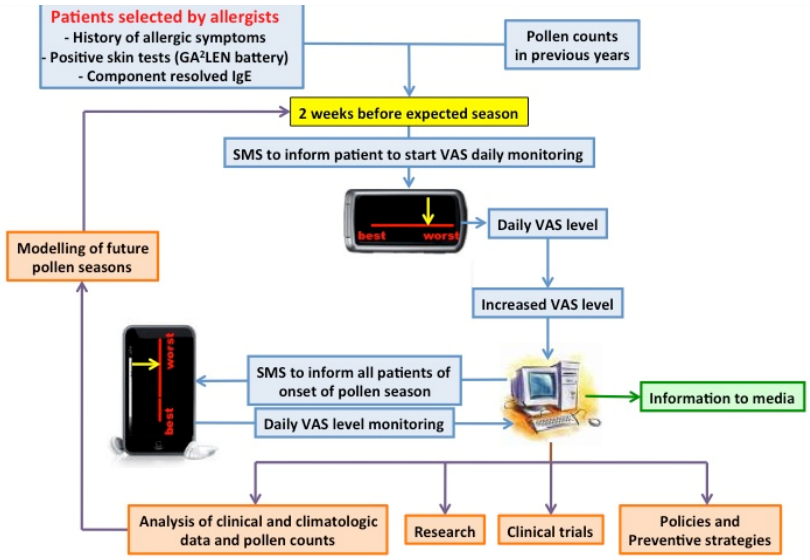


Figure 4: The MASK ICT strategy and usage



3-2- CDSS based on ARIA 2015 to optimize control during allergen exposure and stratification of patients

The chronic respiratory diseases CDSS (AIRWAYS-CDSS) will be based on the ARIA 2015 revision (in preparation) and will enable the standardisation of patient management. Patients with uncontrolled disease based on VAS e-health despite optimal treatment according to guidelines will be considered as SCUAD (severe chronic upper diseases) (15) (Figures 4-6). However, the physicians will determine the strategy to be used for their individual patients. All medications available in the given country are listed in the App according to the IMS list of drugs. The CDSS will be available in the fall of 2015.

These 2 innovative tools (allergy sentinel network and AIRWAYS-CDSS) will be combined in MASK-rhinitis and will make it possible to assess some of the unmet needs of clinical trials in allergic diseases. It will allow optimal management of the patients, assessment of control, compliance to treatment as well as patient stratification.

Figure 5: Screen of the App

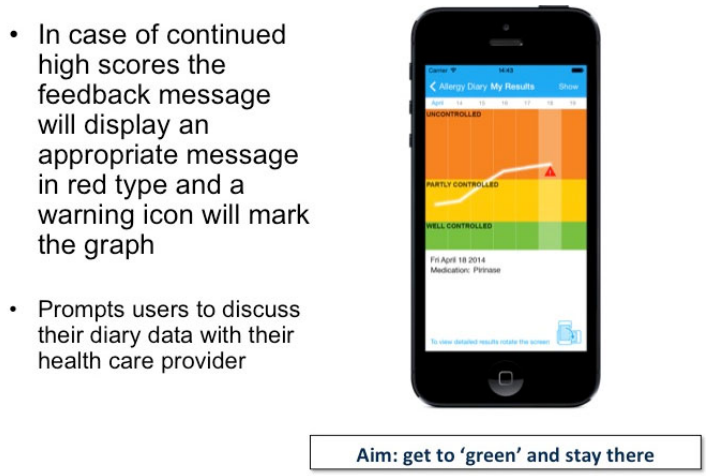
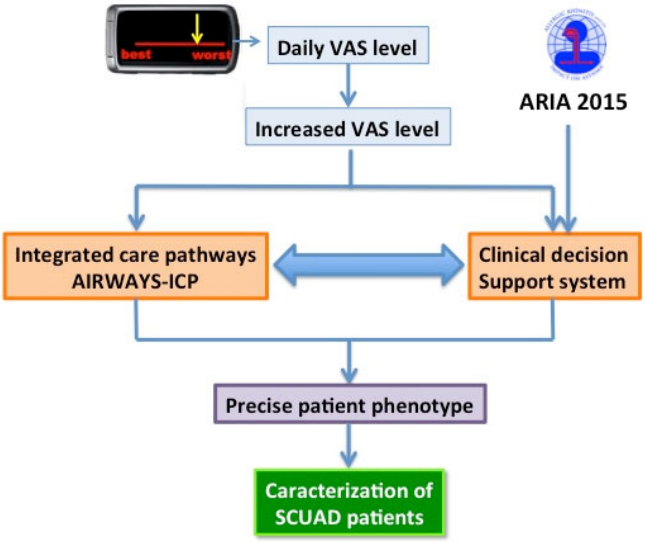


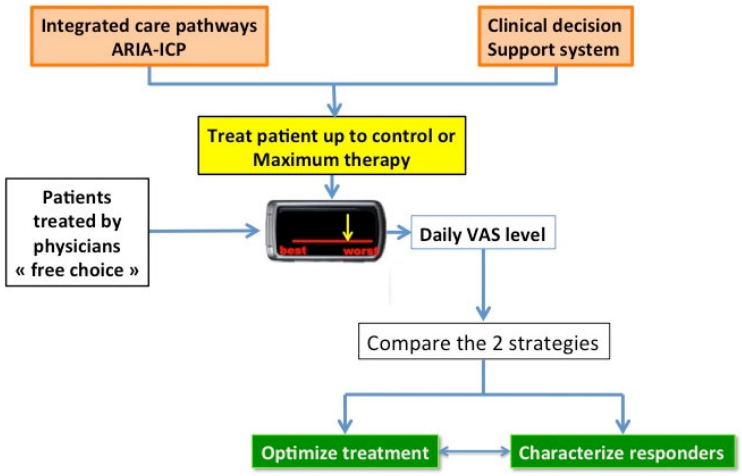
Figure 6: MASK CDSS



3-3- Validation of ARIA guidelines

There is a need to validate guidelines using cluster randomized trials in order to define whether the new strategy is more effective than a free treatment choice. The International Consensus of Rhinitis (102) and ARIA 2001 (103) were both validated. MASK will also be validated using the same methodology (Figure 7).

Figure 7: Validation of MASK in a cluster randomized trial to evaluate guidelines



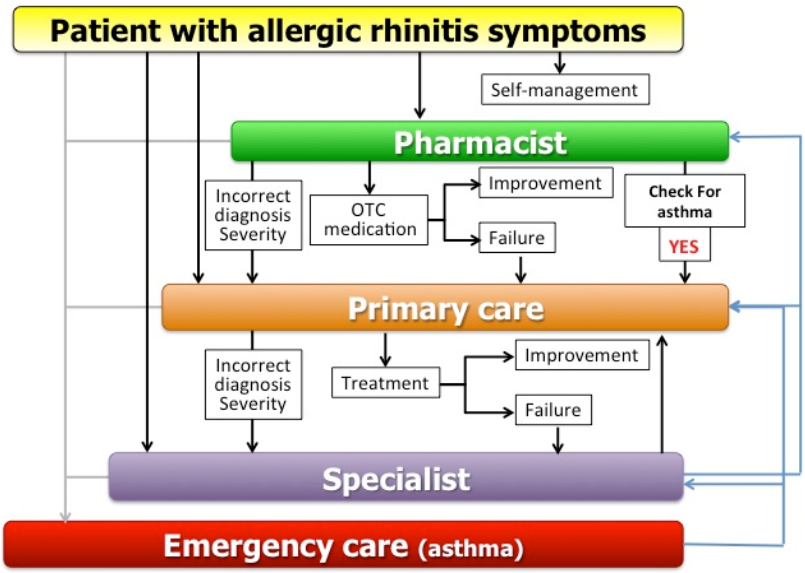
3-4- MASK-rhinitis, a single tool for the ICP

An ICP has a focus on an interactive and multidisciplinary pathway (Figure 8). MASK can be used by:

- Patients, to screen for allergic diseases (in a later stage biomarkers will help to confirm the allergic origin of the symptoms).
- Pharmacists, to guide them in the prescription of OTC medications and direct the uncontrolled patients to physicians.
- The primary care physician, to prescribe appropriate treatment and to follow-up with the patient according to the physician's instructions (CDSS) and assessment of control.
- The specialist, if there is failure to gain control by the primary physician.

These tools should be customized to be applicable globally.

Figure 8: ICP for MASK-rhinitis

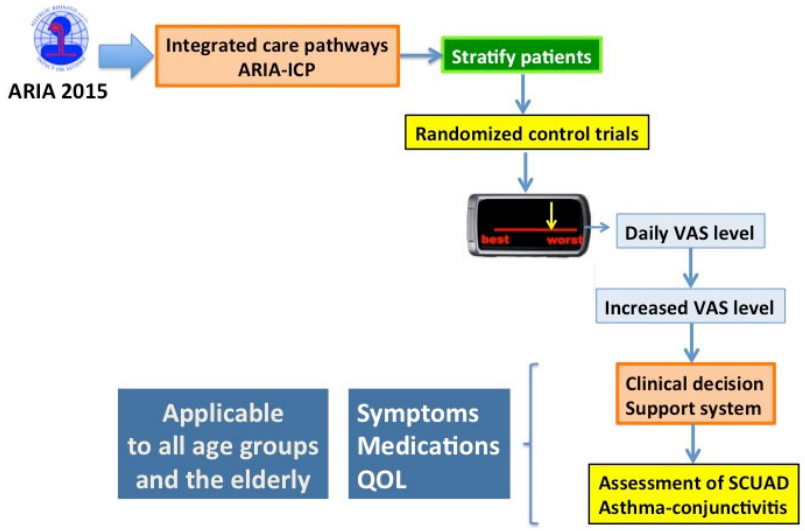


3-5- Clinical trials

These 3 innovative tools (CARAT, allergy sentinel network and AIRWAYS-CDSS) are combined in MASK-rhinitis and will make it possible to perform innovative clinical trials in AR (Figure 9) including trials of allergen-specific immunotherapy (64, 134).

- Phenotypic characterisation of allergic patients with stratification of patient severity, characterisation of SCUAD patients and characterisation of patients to be treated.
- Randomised controlled trials (placebo-controlled or real life cluster randomised trials).
- Follow up of patients in clinical settings during treatment.
- Follow up of patients in clinical settings after treatment has been stopped (persistent effects).
- Assessment of side effects due to treatment.

Figure 9: Clinical trials using MASK-rhinitis.



4- Implementation and application of MASK rhinitis

4-1- Promotion of active and healthy ageing

The developmental origin of ageing is on the EU political agenda. The Polish Priority of the EU Council (2011) promoted the recognition, prevention and management of CRDs in children to ultimately impact AHA (109). The developmental determinants of chronic diseases in ageing were reinforced during the Cyprus Presidency of the EU Council (2012), which proposed to fight against NCDs across the life cycle (135). A meeting at the European Parliament organised by the Region Languedoc Roussillon under the auspices of the Cyprus EU Priority (November 2012) was focused on CRDs (136). MASK-rhinitis will help to detect symptomatic patients early, to improve management, to increase school and work productivity and, ultimately, to promote AHA.

4-2- Early detection of symptomatic patients

One of the major problems of patients suffering from pollen allergy is the identification of the onset of the pollen season at home as well as alertness when pollen peaks are to be expected. Another problem is when travelling to regions where the seasons of pollens eliciting symptoms may differ compared to home (Table 1). Since patients will be geolocalized, they will be informed about the level of the pollen

season and they will also also be able to determine the season when travelling by using MASK-rhinitis.

Table 1: Implications of MASK-rhinitis in early detection of pollen allergy

o Early pre-medical diagnosis o Optimal treatment proposed to control symptoms and prevent severe disease (e.g. asthma exacerbations). o Optimal duration of the treatment. o Reduction of costs incurred by pollen allergy.

4-3- Stratification of patients with severe allergic diseases

Patient stratification is needed to identify SCUAD patients, those for whom specific immunotherapy or other interventions are appropriate. This is critical for the delivery of a cost-effective health system. Although all studies are not consistent, in many diseases, ICT tools, ICPs, e-health and CDSS are likely to define the phenotypes of allergic patients. The main challenge for allergic diseases in the 21st century is to understand their complexity. The vast majority of AR patients can be treated using a simple algorithm. However, a substantial number of these patients are uncontrolled despite treatment (16) and require a personalized (tailored) approach.

4-4- Clinical trials

In specific immunotherapy RCTs, it is recommended to monitor pollen counts in order to determine the onset of the season and to correlate counts with symptoms. As discussed earlier, pollen counts alone may misrepresent exposure, especially if performed at a locality that is remote to that of a particular patient. As a result of such potential confounders, unconvincing data have been produced and a placebo-based method was found to be more effective (137). Moreover, there is a need to define the peak pollen season. MASK-rhinitis is suitable for this approach (64).

4-5- Scientific studies

Not all patients respond to pharmacologic treatment and/or immunotherapy. Research is needed in well-phenotyped patients to find novel therapeutic approaches. MASK-rhinitis can help characterize patients so that they can be stratified in further analyses. Global partnerships and platforms should ensure the application of standard methodology and protocols in the collection and sharing of samples and data (138).

4-6- Assessment of effects of climate changes and land use

Climate change impacts aeroallergens, particularly pollen (139) and molds (140). The potential effect of land use changes on pollen release may interact with climate change (141). Allergenic pollens are well known in Europe (66) but climate change can exert a range of effects on pollen (142-146). Pollination may start earlier in the future due to climate change (147, 148). The duration of the pollen season is extended in some species. Some plants produce a greater quantity of pollen (149-151) or pollen with stronger allergenicity (152-155) under modified climatic conditions. New allergenic pollen types can appear and result in patients developing new allergies (e.g. ragweed pollen). The pattern of change will vary regionally depending on latitude, altitude, rainfall and storms, land-use patterns, urbanization, transportation and energy production (156).

An integrated approach is needed to anticipate a higher allergic disease burden that will affect clinical practice and public health planning. A number of practical prevention strategies need to be proposed to meet this unprecedented public health challenge and to combat inequities. Both adaption and mitigation will be needed to counteract the effects of climate change in allergy (Table 2).

Table 2: Implications of *MASK-rhinitis* in climate changes and land use

- To detect new sensitizations using pollen counts or derived methods.
- To detect changes in pollen seasons.
- To develop policies for prevention.

4-7- Implementation of the European Environment and Health

Continued support will be provided to research addressing the aims of the major policy initiatives such as the European Environment and Health Action Plan (2004-2010), the Fifth Ministerial Conference on Environment and Health, and the EU Sustainable Development Strategy with its environment and public health components. MASK-rhinitis also includes strong socio-economic perspectives. In the medium term, it will ensure the engagement of relevant stakeholders (e.g., user groups, civil society organizations, policy-makers) and it will cultivate a multi-disciplinary approach (including researchers from social sciences and humanities).

4-8- Policies and public health planning

In clinical epidemiology and public health, a uniform definition of AR and severity is needed to identify prevalence, burden and costs, to improve quality of care and to optimize health care planning and policies.

4-9- MASK: from the ARIA 2015 guideline to an integrated health system for allergic rhinitis and its asthma co-morbidity

There is an urgent need to propose an innovative health system for one of the most common disease globally. Around 20% of the EU population suffers from AR and the costs are very high, in particular indirect costs. Although most patients can self-manage their symptoms, many need OTC drugs at the pharmacists and a few (but still in millions of subjects) need a medical advice. Fewer but still in millions will need specialist advice. It is very important that a common language is used from patients to pharmacists, primary care and specialists. MASK is able to provide this common language using e-health and a very simple tool (VAS). Moreover, the CDSS will help patients to self-manage under the control of their physicians. Adding CARAT or other tools, an economic evaluation can be provided to assess the benefits and cost savings (indirect and direct costs) of interventions (5). A warning on asthma is in place in MASK allowing to assess this important co-morbidity in AR patients. Reimbursement patterns can also be monitored and health system stratification possible (157). MASK based on ARIA 2015 appears to be in a unique position to make the links between all stakeholders.

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